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Impaired pituitary response to bromocriptine suppression: reversal after bromocriptine plus tamoxifen

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Abstract. This study was designed to clarify whether previously resistant cases of adenomatous hyperprolactinaemia to bromocriptine might be improved by additive tamoxifen therapy. Ten hyperprolactinaemic women under bromocriptine (2.5–10 mg) with hypophyseal tumours of different extent were treated with a combined therapy of bromocriptine and tamoxifen (10–20 mg). Two of them had undergone incomplete resection of chromophobe adenomata. The others refused surgery or irradiation. Two other women without basal therapy because of side effects from bromocriptine, received the combined therapy from the beginning of the study. In 6 out of 10 women the addition of tamoxifen resulted in a marked suppression of prolactin serum values. Amenorrhoea and glactorrhoea ceased in 4 of them. One woman conceived. One reported a marked improvement of libido. One stated that side effects under bromocriptine disappeared through the addition of tamoxifen. The 2 women who previously were suffering from side effects were able to take bromocriptine when tamoxifen was added. Four patients were non-responders. Serum prolactin remained unchanged as well as the clinical follow-up. The effectiveness of the combined therapy was not related to the extent of the tumour or to the clinical or biochemical baseline date.

We conclude that the suppressive effect of bromocriptine on prolactin secretion is enhanced by the addition of tamoxifen in most cases of adenomatous hyperprolactinaemia. Side effects of bromocriptine are considerably reduced. Anti-oestrogens are competitive inhibitors of the binding of oestradiol to the receptor. Oestrogen play an important role in the development of prolactin secreting adenomata. Our finding of responders and non-responders to tamoxifen suggests that the anti-oestrogen competes for greater or lesser concentrations of receptor sites in prolactinomata.

In experimental animals bromocriptine has been shown to reduce the mitotic rate and size of pituitary tumours (Quadri et al. 1972; Davies et al. 1974; Lloyd et al. 1975; Pawlikowski et al. 1978). Since 1975 these observations have been applied to patients with pituitary tumours. Although documentation often has been scanty, there is radiographic evidence that dopamine agonists, particularly bromocriptine, are effective in reducing the volume of some prolactin-(Prl)-secreting pituitary adenomas (Thorner et al. 1980; Sobrinho et al. 1978; Corenblum 1978; George et al. 1979; Landolt et al. 1979; McGregor et al. 1979). In view of the present state of knowledge it is justified to institute a trial of bromocriptine before surgery or instead of surgery not only in case of microadenoma, but also in those tumours, which are extended beyond the confines of the pituitary fossa (McGregor et al. 1979; Thorner et al. 1980; Eversmann et al. 1979). In patients with macroadenomas with excessive Prl secretion bromocriptine was able to suppress Prl values, and the effect persisted after withdrawal of the substance (Eversmann et al. 1979), indicating that bromocriptine is most effective in tumours with high proliferation rate and high prolactin turnover. Even in case of adenoma

and infertility, some investigators propose bromocriptine therapy instead of surgery. It is wellknown that pregnancy can result in enlargement of a pituitary tumour leading to serious complications, although this seems to be quite rare. Mornex et al. (1978) did not see serious forms of progression during pregnancy in 10 hyperprolactinaemic patients. Shewchuk et al. (1980) reported one case of acute pituitary enlargement in a group of 18 pregnancies.

Nevertheless, in a number of cases suppression of Prl values is poor, even if high dosages of bromocriptine are necessary (> 7.5 mg/d). Occasionally these dosages are intolerable because of side effects, which makes a longer therapy impossible.

There has been considerable effort devoted toward synthesizing other ergot derivatives in order to overcome these difficulties. In this context the studies of De Quijada et al. (1979, 1980) is most interesting, as the authors demonstrated that tamoxifen enhances the sensitivity of dispersed Prl-secreting pituitary tumour cells to bromocriptine. A synergetic effect of dopaminergic drugs and tamoxifen had been reported years before: Di Benedetto et al. (1976) combined tamoxifen and L-dopa in ovariectomized and mastectomized normoprolactinaemic patients with progressive breast cancer and found a marked reduction of Prl values. Wolf et al. (1979) found that bromocriptine converts clomiphene failure in normoprolactinaemic normogonadotrophic amenorrhoea. In 9 of 12 cases the additive therapy with bromocriptine led to a sufficient response to clomiphene.

On the other hand results are conflicting concerning the effect of tamoxifen by itself on Prl secretion (Golder et al. 1976; Mesala et al. 1978; Willis et al. 1977).

The present investigation was undertaken on the assumption that the combined therapy of bromocriptine and tamoxifen might have a synergetic effect in previously resistant cases to brómocriptine monotherapy.

Materials and Methods

Patients

Twelve women from the age of 15 to 54 years were tested. The clinical and baseline Prl values of these women are summarized in Table 1. Two of them (J.K., C.B.) had undergone transsphenoidal surgery for prolactinoma (both Hardy, grade IV (Hardy 1973)), but the removal of the tumour had been incomplete. Prl values were suppressible by bromocriptine but both women refused medication because of side effects (vomiting, headaches, fainting). The other 10 women were under long-term bromocriptine therapy (2.5–10 mg daily). Seven had sellar or suprasellar enlargements (Hardy, grade I–III), 3 of them having undergone incomplete surgical resection. Surgery was refused by the patients with macroadenomata. The others had normal sella tomograms, but high Prl levels. In these women standard dosages of bromocriptine (5–7.5 mg/d) did not cause suppression of Prl levels, while increased dosages had been refused due to the side effects. Therefore in these patients pituitary tumours had been suspected. Patient No. 6 (M.V.) had to reduce her dosage to 2.5 mg 16 weeks before the beginning of the study.

Previously she had been under 5 mg for 8 weeks (Prl: 33.4 ng/ml before the reduction).

Protocol of investigation; assays

All patients had polytomography of the sella turcica, 8 women (patient Nos. 1, 2, 3, 7, 8, 9, 10, 11) additionally had computerized tomography of the skull (CT). In all patients the visual fields were examined.

In case No. 2 suprasellar enlargement was detected by CT, while hemianopsia on the right side was seen later. In case No. 7 bitemporal hemianopsia was already known, when she presented herself for the first time. LH, FSH, oestradiol (E_2), Prl were measured by radioimmunoassays. Prl and FSH were determined by the 'Serono'-kits (double-antibody-radioimmunoassay). LH and E_2 were measured in duplicate by radioimmunoassay systems as described elsewhere (Saxena et al. 1969; England et al. 1974), using charcoal for B/F-separation of E_2 and a second antibody for separation of LH. At the beginning of the study six morning blood samples at 15 min intervals were obtained between 08.00–10.00 for the measurement of the above mentioned hormones. Afterwards each patient started a combined therapy of bromocriptine (Pravidel®, 2.5–7.5 mg) plus tamoxifen (Nolvadex®, 10–20 mg). This procedure of hormone controls was repeated 1 week later and again after a further 3 weeks had elapsed. Side effects or reduction of formerly mentioned side effects were noted. Basal body temperature (BBT) and the development of previously noted galactorrhoea or additional complaints were carefully reported. In Tables 2–4 the hormonal changes as well as the clinical follow-up are depicted.

Statistical evaluation

The hormone values of each patient before and under combined therapy were compared by a grouped two-tailed *t*-test (Tables 3 and 4). In case of low hormone values (Prl < 2 ng/ml; E_2 < 10 pg/ml) the Mann-Whitney test was used. In a second statistical step the mean Prl values are listed 1 and 4 weeks after the beginning of tamoxifen medication as percentage deviations from the initial values under bromocriptine monotherapy.

Table 1.

Baseline clinical data of 12 women with tumourous hyperprolactinaemia. In case No. 4–6 tumour suspected because of clinical follow-up, see text. Prl values before medication of bromocriptine.

Case No.	Age	Births abortions	Tumour-grading (Hardy 1973)	Symptoms duration (years)	Special items (duration/years)	Prl (ng/ml)
1 (B.V.)	37	0/0	III	amenorrhoea (14), galactorrhoea (12)	incompl. resection of chrom. ademoma 2 years before	580.0
2 G.W.)	46	0/0	II + suprasellar extension loss of libido (12)	amenorrhoea (28), hemianopsia (2),	hemianopsia dextra (2)	130.6
3 (H.G.)	31	1/1	III	amenorrhoea (7)	incompl. resection of chrom. adenoma 2 years before	1580.0
4 (I.G.)	18	0/0	–	amenorrhoea (4), galactorrhoea (3)		210.3
5 (T.T.)	53	1/0	–	galactorrhoea (12)		295.6
6 (M.V.)	31	1/0	–	amenorrhoea (15), galactorrhoea (15)		156.6
7 (J.K.)	45	2/0	IV	amenorrhoea (10), galactorrhoea (10), hemianopsia (2)	incompl. resection of chrom. adenoma 12 months before bit. hemianopsia (~ 2)	> 2000.0
8 (C.B.)	27	0/1	IV	amenorrhoea (7), galactorrhoea (7)	incompl. resection of chrom. adenoma 10 months before	1200.0
9 (M.B.)	39	1/0	II	amenorrhoea (12), galactorrhoea (15)	incompl. resection of chrom. adenoma 16 months before	630.4
10 (S.B.)	20	0/0	III	oligomenorrhoea (5), galactorrhoea (2)		750.2
11 (M.I.)	27	1/0	I	amenorrhoea (2)		456.6
12 (D.H.)	24	0/0	I	amenorrhoea (7)		106.0

Results

Table 2 presents the clinical follow-up of the 12 women receiving bromocriptine plus tamoxifen. On the basis of clinical and biochemical data the patients were divided into two major groups: responders and non-responders. Noticeable declines of Prl values occurred in 8 cases. Two of them have to be partly excluded (case Nos. 7, 8), as bromocriptine suppression was principally possible but not accepted because of heavy side effects of the drug. Nevertheless, it is significant that the substance was tolerated, when tamoxifen was added. In the other 6 cases the decline of Prl was accompanied by clinical improvement: amenorrhoea ceased in 4 out of 5 women, galactorrhoea in 4 (case No. 5 was post-menopausal). Case No. 2 reported re-appearance of libido after decades of frigidity.

During tamoxifen therapy one woman conceived (case No. 1) after 12 years of sterility. Similar to case Nos. 7, 8 one woman (case No. 6) reported that side effects of bromocriptine disappeared, when tamoxifen was added. Four women were non-responders. Neither Prl values nor clinical follow-up

Table 2.

Clinical follow-up of 10 women with insufficient Prl suppression under bromocriptine and of 2 women (J. K., C. B.), in which bromocriptine therapy had to be stopped because of heavy side effects.

Case No.	Age	Tumour-grading (Hardy 1973)	Symptoms, special items	Basal Prl (ng/ml)	Basal therapy (duration/months)	Prl c the (ng/ml)
Responders to additive tamoxifen therapy						
1 (B.V.)	37	III	amenorrhoea, galactorrhoea incompl. resection of chrom. adenoma infertility	580.0	bromocriptine 10 mg (10)	70.1
2 (G.W.)	46	II + suprasellar extension	amenorrhoea, hemianopsia dextra, loss of libido	130.6	bromocriptine 5 mg (5)	22.9
3 (H.G.)	31	III	amenorrhoea after incompl. resection of chrom. adenoma	1580.0	bromocriptine 5 mg (22)	322.(
4 (I.G.)	18	–	amenorrhoea, galactorrhoea	210.3	bromocriptine 5 mg (12)	33.4
5 (T.T.)	53	–	galactorrhoea	295.6	bromocriptine 5 mg (36)	56.(
6 (M.V.)	31	–	amenorrhoea, galactorrhoea	156.6	bromocriptine 2.5 mg (16)	42.5
7 (J.K.)	45	IV	amenorrhoea, galactorrhoea, bit. hemianopsia, incompl. resection of chrom. adenoma	> 2000.0	none (side effects)	1010.(
8 (C.B.)	27	IV	amenorrhoea, galactorrhoea, incompl. resection of chrom. adenoma	1200.0	none (side effects)	170.
Non-responders						
9 (M.B.)	39	II	amenorrhoea, galactorrhoea after incompl. resection of chrom. adenoma	630.4	bromocriptine 5 mg (12)	58.
10 (S.B.)	29	III	oligomenorrhoea, galactorrhoea	750.2	bromocriptine 5 mg (25)	33.
11 (M.T.)	27	I	amenorrhoea	456.6	bromocriptine 5 mg (10)	152
12 (D.H.)	24	I	amenorrhoea	106.0	bromocriptine 5 mg (6)	22

were influenced by the addition of tamoxifen. Tables 3 and 4 show the values of Prl, LH, FSH, and E_2 (mean (SD)); (case Nos. 4, 7, 8: single values). In 2 cases (case Nos. 9, 11) LH and FSH serum levels were elevated under the anti-oestrogen, in one of them (case No. 9) with significant stimulation of the ovary (elevated serum E_2). There were no statistical differences between responders and non-responders concerning basal E_2 and Prl ($P \leq 0.05$). The groups cannot be related to the extension of the tumours, although the responder group contains case Nos. 4, 5, 6, which were suspected to have very small tumours. In one case (M.V.) one half of the usual dose (bromocriptine 2.5 mg, tamoxifen 10 mg) was effective, too. In the responder group the positive action of tamoxifen

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Basal therapy ration/months)	Prl during therapy (ng/ml) mean (SD)	Combined therapy (4 weeks)	Prl after 4 weeks comb. therapy (ng/ml) mean (SD)	Result of therapy
riptine 10 mg (10)	70.1 (11.4)	bromocriptine 10 mg tamoxifen 20 mg	23.4 (4.1)	cessation of galactorrhoea, conception 2 weeks after the test period
riptine 5 mg (5)	22.9 (2.5)	bromocriptine 5 mg tamoxifen 20 mg	5.7 (0.4)	ovulatory cycles improvement of libido
riptine 5 mg (22)	322.0 (34.1)	bromocriptine 5 mg tamoxifen 20 mg	24.9 (3.9)	oligomenorrhoea
riptine 5 mg (12)	33.4	bromocriptine 5 mg tamoxifen 20 mg	13.1	cessation of galactorrhoea, ovulatory cycles
riptine 5 mg (36)	56.6 (4.1)	bromocriptine 5 mg tamoxifen 20 mg	12.8 (1.5)	cessation of galactorrhoea,
riptine 2.5 mg (16)	42.5 (4.6)	bromocriptine 5 mg	12.3 (0.6)	cessation of galactorrhoea, oligomenorrhoea, bromocriptine tolerated
ide effects)	1010.0	bromocriptine 5 mg tamoxifen 20 mg	38.0	cessation of galactorrhoea, no side effects under bromocriptine
ide effects)	170.0	bromocriptine 5 mg tamoxifen 20 mg	10.3	cessation of galactorrhoea, ovulatory cycles, bromocriptine tolerated
riptine 5 mg (12)	58.9 (19.7)	bromocriptine 5 mg tamoxifen 20 mg	43.8 (1.8)	persistence of amenorrhoea, galactorrhoea
riptine 5 mg (25)	33.0 (3.6)	bromocriptine 5 mg tamoxifen 20 mg	43.9 (12.7)	no improvement
riptine 5 mg (10)	152.0 (10.3)	bromocriptine 5 mg tamoxifen 20 mg	134.5 (13.3)	persistence of amenorrhoea
criptine 5 mg (6)	22.6 (2.2)	bromocriptine 5 mg tamoxifen 20 mg	44.3 (28.6)	intermittent uterine bleeding

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on Prl secretion was seen after the first week of treatment, but in all these cases the effect was further improved after 4 weeks (Table 3). Fig. 1 shows the deviation of the mean percentage values, indicating the divergent effects of tamoxifen addition on Prl values with clear preponderance of the responder group.

Discussion

Although in recent years selective removal of pituitary microadenomas has become a relatively low-risk procedure (Wiebe et al. 1979), the beneficial effects of alternative bromocriptine treatment have been widely documented (Mornex et al. 1978;

Table 3.

Prl and E_2 under bromocriptine (0 weeks) and under 1 and 4 weeks combined therapy with bromocriptine plus tamoxifen. Difference of values is significant, if $P < 0.05$.

Case No.	0 weeks	*P*	1 week	*P*	4 weeks	% *P*
Prl (ng/ml)						
1 (B.V.)	70.1 (11.4)	0.01	46.1 (13.6)	0.004	23.4 (4.1)	0.0001
2 (G.W.)	22.9 (2.5)	0.0001	12.3 (3.4)	0.002	5.7 (0.4)	0.0001
3 (H.G.)	322.0 (34.1)	0.0001	51.6 (22.5)	0.02	24.9 (3.9)	0.0001
4 (I.G.)	33.4		22.3		13.1	
5 (T.T.)	56.5 (4.1)	0.0001	15.2 (0.6)	0.02	12.8 (1.5)	0.0001
6 (M.V.)	42.5 (4.6)	0.0001	24.7 (7.1)	0.003	12.3 (0.6)	0.0001
7 (J.K.)	1000		–		38.0	
8 (C.B.)	170.0		–		10.3	
9 (M.B.)	58.9 (19.7)	0.2	46.3 (5.0)	0.3	43.8 (1.8)	0.1
10 (S.B.)	33.0 (3.6)	0.6	34.5 (5.1)	0.2	43.9 (12.7)	0.2
11 (M.T.)	152.0 (10.3)	0.2	142.3 (13.3)	0.4	134.5 (13.3)	0.2
12 (D.H.)	22.6 (2.2)	0.1	27.3 (5.6)	0.2	44.3 (28.6)	0.1
E_2 (pg/ml)						
1 (B.V.)	41.1 (9.9)	0.002	101.8 (28.6)	0.02	158.7 (36.8)	0.0001
2 (G.W.)	187.3 (29.8)	0.2	150.3 (44.7)	0.7	139.2 (44.3)	0.1
3 (H.G.)	–		10.0	0.0001	204.5 (21.2)	
4 (I.G.)	62.0		–		363.3	
5 (T.T.)	19.1 (7.7)	0.6	17.1 (4.6)	0.7	19.6 (12.0)	0.95
6 (M.V.)	71.6 (16.4)	0.0001	225.5 (34.7)	0.1	270.4 (42.1)	0.0001
7 (J.K.)	–		–		–	
8 (C.B.)	79.4		–		–	
9 (M.B.)	21.9 (11.9)	0.002	91.9 (31.8)	0.03	137.2 (28.2)	0.0001
10 (S.B.)	80.4 (37.8)	0.9	87.0 (15.5)	0.6	97.7 (44.1)	0.8
11 (M.T.)	75.8 (10.8)	0.7	79.4 (14.4)	0.1	62.4 (7.1)	0.1
12 (D.H.)	76.0 (18.2)	0.05	98.5 (15.3)	0.9	100.0 (21.0)	0.1

Shewchuk et al. 1980). On the other hand there are clinical courses, which are unsatisfactory.

Firstly, there are cases of incomplete suppression through bromocriptine, when very high dosages are required but not tolerated by the patients.

Secondly, some women, in which suppression of Prl is difficult to obtain with bromocriptine, refuse surgery.

Thirdly, there are cases with incomplete resection of prolactinomas and tumour rest.

In all these cases heavy side effects of the drug may be a limiting factor.

The purpose of this study was to decide whether the in vitro sensitizing effects of tamoxifen on pituitary tumour cells together with bromocriptine (de Quijada et al. 1980) was applicable to in vivo situations. To our knowledge this report is the first demonstration that in most cases the suppressive effect of bromocriptine on Prl secretion is markedly enhanced by the addition of tamoxifen in women. However, 4 out of 10 women were non-responders. The effectiveness of the anti-oestrogen was not related to the extension of the tumour or to clinical or biochemical baseline data. Pichon et al. (1980) demonstrated that many, but not all, human pituitary adenomas contain oestrogen receptors in the cytosol. The fact that not all pituitary adenomas are stimulated by oestrogens may be related to that finding. There are cases of excessive tumour growth under high endogenous oestrogens in pregnancy (Kajtar & Tomkin 1971; Child et al. 1975). Others have insignificant or no alterations at all (Mornex et al. 1978). On the other hand prolactinomas under low oestrogens as in males are often

with bromocriptine

ks	% P
.1)	0.0001
.4)	0.0001
.9)	0.0001
.5)	0.0001
.6)	0.0001
.8)	0.1
2.7)	0.2
3.3)	0.2
8.6)	0.1
5.8)	0.0001
4.3)	0.1
1.2)	
2.0)	0.95
2.1)	0.0001
3.2)	0.0001
1.1)	0.8
1)	0.1
..0)	0.1

Table 4.

LH and FSH under bromocriptine (0 weeks) and under 1 and 4 weeks combined therapy with bromocriptine plus tamoxifen. Difference of values is significant, if $P < 0.05$.

Case No.	0 weeks	P	1 week	P	4 weeks	% P
LH (mIU/ml)						
1 (B.V.)	8.2 (2.4)	0.02	12.5 (2.4)	0.3	15.1 (5.0)	0.02
2 (G.W.)	10.3 (1.7)	0.2	11.9 (1.4)	0.1	17.2 (6.0)	0.03
3 (H.G.)	7.1 (0.8)	0.0001	10.8 (0.9)		–	
4 (I.G.)	5.8		–		5.5	
5 (T.T.)	50.0 (13.2)	0.9	49.1 (6.1)	0.8	47.5 (9.5)	0.8
6 (M.V.)	6.9 (0.5)	0.0001	11.5 (1.6)	0.002	16.6 (2.0)	0.0001
7 (J.K.)	–		–		–	
8 (C.B.)	10.4		–		–	
9 (M.M.)	8.0 (0.5)	0.02	11.5 (3.0)	0.0001	21.1 (1.5)	0.0001
10 (S.B.)	18.6 (1.5)	0.2	16.8 (2.5)	0.6	15.6 (3.9)	0.2
11 (M.T.)	9.0 (0.7)	0.05	8.0 (0.8)	0.0001	19.5 (3.0)	0.0001
12 (D.H.)	12.3 (4.8)	0.2	15.9 (4.2)	0.1	12.0 (2.6)	n. s.
FSH (mIU/ml)						
1 (B.V.)	7.0 (1.9)	0.9	6.8 (1.9)	0.7	7.3 (1.4)	0.8
2 (G.W.)	5.3 (1.3)	0.1	4.6 (1.0)	0.002	5.9 (0.5)	0.3
3 (H.G.)	2.0	0.004	3.8 (0.7)		–	
4 (I.G.)	–		–		–	
5 (T.T.)	48.4 (10.9)	0.9	47.2 (7.4)	0.3	55.6 (15.7)	0.4
6 (M.V.)	2.3 (0.1)	0.02	4.1 (1.1)	0.03	7.3 (2.9)	0.01
7 (J.K.)	–		–		–	
8 (C.B.)	–		–		–	
9 (M.M.)	2.6 (0.4)	0.0001	4.0 (0.5)	0.0001	5.9 (0.5)	0.0001
10 (S.B.)	4.9 (1.1)	0.03	3.6 (0.5)	0.002	5.4 (0.8)	0.4
11 (M.T.)	4.3 (0.6)	0.6	4.0 (1.0)	0.0001	13.2 (2.2)	0.0001
12 (D.H.)	3.5 (0.4)	0.0001	5.3 (0.6)	0.0001	2.9 (0.7)	0.2

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large and proliferative (Peillon et al. 1977). The mechanism of long acting anti-oestrogens like tamoxifen is still poorly understood, but it has been proven that these compounds are competitive and total inhibitors of the binding of E_2 to the oestrogen receptor (Borgna et al. 1979). This competition for greater or lesser concentration of receptor sites in prolactinomas may be responsible for our finding that there are responders and non-repsonders to additive tamoxifen therapy. Basal serum concentration of E_2 or the extent of the tumour cannot be taken into account for this dual mechanism, since both groups had low and normal E_2 serum levels and different tumour grading (Tables 1 and 4). Anti-oestrogens have an intrinsic oestrogen-like action which has to be taken into account, too, for the enhanced bromocriptine effect. In hypophyseal stalk dissected rhesus monkeys the dopamine suppression of prolactin is increased under exogenous oestrogens (Neill et al. 1981). The same effect has been observed in women during follicular maturation. The Prl suppressive effect of dopamine infusions was reduced in ovariectomized women (Judd et al. 1979). Two of the 4 cases with unchanged Prl levels had a marked elevation of gonadotrophins, one of them with secondary stimulation of the ovary. But there was no uterine bleeding afterwards. This corresponds well to the known high proportion of clomiphene failure in patients suffering from hyperprolactinaemia. Schneider & Bohnet (1977) reported maintained circhoral LH-fluctuation and LH-surge after clomiphene in hyperprolactinaemic women but with insufficient corpus luteum.

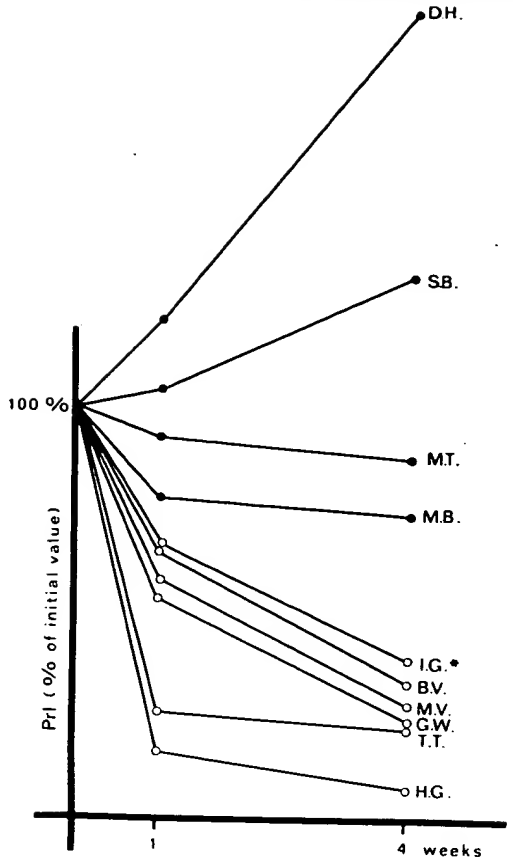

Fig. 1.
Prolactin values as percentage deviation from the initial values under bromocriptine (mean values, asterisk: single value). Open circles: responders to additive tamoxifen therapy. Closed circles: non-responders. Case Nos. 7, 8 (J.K., C.B.) are omitted, see text.

Three cases had suffered from side effects under bromocriptine. In these women the additive therapy with tamoxifen was followed by a marked (and surprising) improvement of the acceptance of bromocriptine. Up to now no explanation can be given for this effect. In subsequent studies it will be interesting to examine whether this is a common effect and if so, to give an explanation for it.

Finally it should be mentioned that long-term therapy of tamoxifen has to be considered as innoxious. Healthy pre-menopausal women under long-term application (20 mg/d) continued to have regular menstruations with biphasic basal body temperature records (Sherman et al. 1978). The manufacturers advise against giving tamoxifen after the onset of pregnancy. In the experiments with rats, rabbits, and mice anti-oestrogens have been shown to have an antifertility effect when given in early pregnancy (Harper & Walpole 1966; Barnes & Meyer 1962; Davidson et al. 1965; Furr et al. 1976). Eneroth et al. (1971) observed hydramnios and cataracts in rats. In human, anti-oestrogens increase multiple pregnancy rates, but there is no evidence of a hightened incidence of congenital malformations (Tuchmann-Duplessis 1977).

The foregoing data confirm that in most cases of tumourous hyperprolactinaemia the suppressive effect of bromocriptine on Prl secretion is enhanced by a combined therapy with tamoxifen. It seems that side effects of bromocriptine are considerably improved by the addition of tamoxifen.

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